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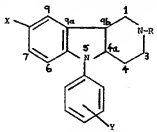
## (54) PYRIDO-INDOLE TRANQUILISING AGENTS


(71) We, PFIZER INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-


This invention relates to *trans*-5-aryl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole derivatives and in particular to certain *trans*-2-substituted-5-aryl-2,3,4-,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole derivatives, useful as tranquilising agents. The invention is also concerned with the preparation of said *trans*-2-substituted-5-aryl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indoles and pharmaceutical compositions containing them.

Following the introduction of reserpine and chlopromazine in psychotherapeutic medicine in the early 1950's, great effort has been expended in the search for other tranquilising agents having improved biological profiles, several of which are γ-carboline derivatives, also known in the art as derivatives of pyrido[4,3-b]indole. In particular our British Patent Specification No. 1476087 discloses certain 2-substituted 5-aryl-1,2,3,4-tetrahydro-γ -carboline derivatives as tranquilising agents. It has now, unexpectedly, been found that the *trans*-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indoles of the present invention have markedly superior tranquilising activity when compared with the corresponding 1,2,3,4-tetrahydro-γ -carbolines.

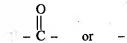
Thus, according to the present invention there are provided 2-substituted-5-aryl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indoles of the formula (I):



... (I)

and the pharmaceutically-acceptable salts thereof, wherein the hydrogen atoms in the 4a position and 9b position are in a *trans* relationship to each other and X and Y are the same or different and are each hydrogen or fluoro; R is $CH_3$, or a group of the formula

wherein n is 3 or 4, m is 2 or 3, M is



and Z is hydrogen, fluoro or methoxy; provided that when R is $CH_3$ at least one of X and Y is fluoro and when R is

Z is not hydrogen.

The invention further provides methods for the treatment of schizophrenic manifestations in non-human mammals which comprises orally or parenterally administering to a non-human mammal in need of such treatment a tranquilising amount of a compound of the formula (I).

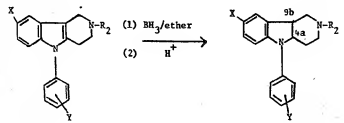
Also provided are pharmaceutical compositions active as tranquilising agents comprising a pharmaceutically acceptable carrier and a compound of the formula (I).

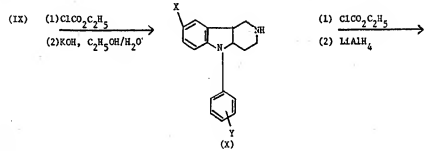
The compounds of the present invention have a markedly and unexpectedly superior tranquilising effect over the above mentioned tranquilising agents of the prior art.

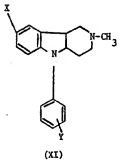
Especially preferred transquilising agents of the invention are the enantiomers and racemic mixtures of:

*trans*-8-fluoro-5-(*p*-fluorophenyl)-2-methyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido-[4,3-b]indole,
*trans*-8-fluoro-5-(*p*-fluorophenyl-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*trans*-5-phenyl-2-[4-hydroxy-4-(*p*-methoxyphenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-]indole,
*trans*-8-fluoro-5-(*p*-fluorophenyl-2-[4-hydroxy-4-(*p*-methoxyphenyl)butyl] 2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*trans*-5-phenyl-2-(4-hydroxy-4-phenylbutyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido-[4,3-b]indole,
*trans*-8-fluoro-5-(*p*-fluorophenyl)-2-(4-hydroxy-4-phenylbutyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*trans*-5-phenyl-2-[3-(*p*-fluorobenzoyl)propyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido-[4,3-b]indole,
*trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[3-(*p*-fluorobenzoyl)propyl]2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-(*p*-fluorophenyl)-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-(*p*-methoxyphenyl-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*trans*-8-fluoro-5-(*o*-fluorophenyl-2-[4-hydroxy-4-*p*-fluorophenyl)butyl]-2,3,4,4a,5,9bl-hexahydro-1H-pyrido [4,3-b]indole,
*trans*-5-phenyl-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*trans*-8-fluoro-5-(*o*-fluorophenyl-2-[4-(*p*-fluorophenyl)-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

The following reaction scheme is illustrative of the processes which may be employed for synthesis of the 4a,9b-*trans*-2-methyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido [4,3-b] indoles of formula (I) wherein R is methyl and X and Y are as previously defined:




A preferred value for $R_2$ is benzyl for reasons of economy. However, other values of $R_2$ which will also serve in the above scheme will be obvious to those skilled in the art. Examples of such alternate values for $R_2$ are benzyl moieties substituted in the benzene ring by, for example, one or more members selected from the group consisting of methyl, methoxy, nitro and phenyl; and benzhydryl.

The reduction of the tetrahydro-γ-carbolines of formula (VIII) to form the 4a, 9b-*trans*-hexahydro compounds of the formula (IX) is carried out in an ether solvent, usually tetrahydrofuran. In order to assure complete reduction a molar excess of borane/tetrahydrofuran complex (BH·THF) is ordinarily employed and a 100 to 200% molar excess of said complex is preferred. While the reaction may be carried out at a temperature in the range of about −10 to 80°C., a temperature of from about 0 to 65°C. is preferred. Ordinarily, a solution of the starting material of formula (VIII) in tetrahydrofuran is added to an ice-cooled solution of $BH_3$·THF. After the addition is complete the reaction mixture is heated to reflux and maintained at this temperature for a period of about one to two hours or more. The reaction is ordinarily carried out in the presence of an inert gas such as nitrogen. When the reaction is substantially completed, the solvent is evaporated and the residue is acidified with an excess of an acid such as, for example, 2 to 12 molar hydrochloric acid. A preferred acidulant is a mixture of equal volumes of acetic acid and 5 molar hydrochloric acid. The acidified mixture is ordinarily heated at reflux for 1 to 2 hours or more. The desired product may then be isolated, for example, by evaporation of any residual ether solvent and a portion of the acid mixture and the precipitated product collected by filtration and washed. In an alternate method of isolation of the product (IX), after the reflux period the reaction mixture is filtered, the filtrate cooled and made alkaline by addition of, for example, sodium hydroxide, potassium hydroxide or sodium carbonate. The basic mixture is extracted with a water immiscible organic solvent such as, for example,

chloroform, methylene chloride or benzene, the extracts evaporated and the residue purified by silica gel column chromatography, eluting, for example, with ethyl acetate or mixtures of hexane/ethyl acetate.

The reduction of tetrahydro-γ-carbolines by $BH_3$·THF followed by acid treatment yields hexahydro-γ-carbolines in which the hydrogens attached to the carbon atoms in the 4a and 9b positions are in a *trans*-relationship, see, for example, U.S. 3,991,199.

The 2-benzyl compounds of formula (IX) are then converted to the corresponding 2-hydrogen compounds of formula (X). In general, this may be accomplished by treating the compound of formula (IX) with a molar excess of a lower alkyl chloroformate ester such as, for example, the methyl, ethyl, propyl or isobutyl ester in the presence of a suitable reaction-inert organic solvent, followed by alkaline hydrolysis. Preferred as chloroformate ester is ethyl chloroformate because of its ease of availability and efficiency. By a suitable reaction-inert organic solvent is meant one which will substantially dissolve the reactants under the conditions of the reaction without the formation of byproducts. Examples of such solvents are aromatic hydrocarbons such as benzene, toluene and xylene; chlorinated hydrocarbons such as chloroform and 1,2-dichloroethane, diethyleneglycol dimethylether and dimethylsulfoxide. An especially preferred solvent is toluene.

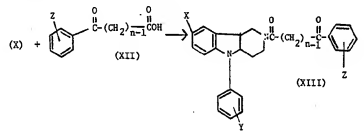
To the mixture of starting material of formula (IX) in said reaction inert organic solvent is added up to about a ten molar excess of the chloroformate ester. For reasons of economy a molar excess of about 3 to 5 is preferable. The resulting mixture is then heated at a temperature of from about 80-150°C., typically at the reflux temperature of the mixture, for periods of about 6 to 24 hours or more. Ordinarily, refluxing is carried out overnight for reasons of convenience. The reaction mixture is then evaporated *in vacuo* and the residue taken up an alcohol-water mixture, an alkali, for example, sodium hydroxide or potassium hydroxide, is added in about 10-30 molar excess based on the amount of starting material of formula (IX), and the resulting mixture heated at reflux, typically overnight. The solvent is then evaporated and the residue partitioned between water and a water immisible organic solvent such as, for example, chloroform, methylene chloride or ethyl ether and the organic phase evaporated to dryness. The residual product of formula (X) may be used as is or further purified by standard methods known in the art, for example, by column chromatography on silica gel.

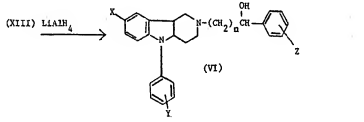
In the case of compounds of the formula (IX) wherein both X and Y are hydrogen and $R_2$ is benzyl, the corresponding compound of formula (X) may be obtained by catalytic debenzylation employing hydrogen and a palladium-on-carbon catalyst. The reaction is typically carried out employing the hydrochloride salt of the compound (X) at a temperature of from about 50 to 100°C, preferably 60-75°C, and hydrogen pressures of about 20-100 p.s.i. (1.4-7 kg/cm$^2$) in the presence of a reaction-inert solvent, for example, methanol, ethanol, isopropanol, ethyl acetate or mixtures thereof with water. When the hydrogen uptake is complete, the catalyst is removed by filtration and the hydrochloride salt of the product of formula (X) is precipitated by addition of a nonsolvent, for example, ethyl ether, benzene or hexane. Alternatively, the free base of formula (X) may be isolated by evaporating the filtrate from the debenzylation of dryness, partitioning the residue between aqueous alkali, for example sodium hydroxide, and a solvent such as chloroform on ethyl ether. The free base is then isolated by standard methods such as those described above.

The intermediates of formula (X) may then be converted to the desired 2-methyl compounds (XI), by acylation with a chloroformate ester, preferably ethyl chloroformate, followed by reduction of the intermediate 2-alkoxycarbonyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole with lithium aluminium hydride. The reaction with, for example, ethyl chloroformate and compound of formula (X) is carried out, under substantially anhydrous conditions, in the presence of a reaction-inert organic solvent such as chloroform, methylene chloride, tetrahydrofuran or ethyl ether and preferably in the presence of a tertiary amine such as, for example, pyridine, triethylamine or N,N-dimethylaniline. To a solution of the compound of formula (X) in said solvent, optionally containing a molar excess of said tertiary amine, is added an approximately equimolar amount of the chloroformate ester. After the addition the reaction mixture is stirred for a period of up to a few hours. The reaction is ordinarily carried out at or about room temperature, however, higher or lower temperatures from about 0°C. up to the reflux temperature of the solvent will suffice. When ethyl chloroformate is employed, the intermediate 2-ethoxycarbonyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole intermediate is isolated by methods which will be apparent to one skilled in the art, such as, for example, evaporation of the reaction mixture to dryness, partitioning of the residue between a water immiscible organic solvent such as ethyl ether, chloroform or dichloromethane, and a dilute aqueous acid such as hydrochloric or sulfuric acids. The organic extracts are washed with water, dried, and evaporated to dryness to afford a product suitable for use in the hydride reduction step.

The reduction is preferably carried out in the presence of an inert gas such as nitrogen or argon and under substantially anhydrous conditions. From about 2 to 10 molar excess of lithium aluminum hydride is suspended in an ethereal solvent, for example, ethyl ether or tetrahydrofuran and the mixture is preferably cooled to a temperature of about 0 to 10°C. The intermediate 2-alkoxycarbonyl product, obtained as described above, is ordinarily dissolved in the same solvent and the solution added dropwise. The resulting mixture is then reacted, ordinarily at or about room temperature for a period of from about 0.5 to 4 hours to attain substantial completion of the reaction. The excess lithium aluminum hydride is then decomposed, e.g., by cautious addition of water, the resulting mixture filtered and the filtrate evaporated to dryness to provide the desired product of formula (XI) which may be further purified, if desired, by standard methods known to one skilled in the art. Alternatively, the free base, (XI), may be converted to a salt such as, for example, the hydrochloride addition salt by addition of anhydrous hydrogen chloride to a solution of the base in a solvent such as ethanol, ethyl ether or mixtures thereof. The precipitated salt may then be collected, e.g., by filtration.

The free bases of formula (X) may also serve as precursors for the novel compounds of formula (VI) as illustrated by the following reaction sequence wherein X, Y, Z and n are as previously defined.

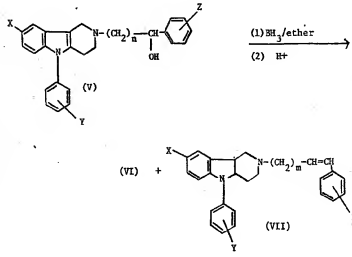




The acylation of the compounds (X) to form the intermediates of formula (XIII) may employ the acids of formula (XII) or the corresponding acid chlorides or acid bromides. When the acids of formula (XII) are employed in the acylation, approximately equimolar amounts of said acid and compound of formula (X) are contacted in the presence of a reaction-inert organic solvent and certain condensing agents known in the art for forming peptide bonds. Such agents include carbodiimides, for example, dicyclohexylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, and alkoxyacetylenes, for example, methoxyacetylene and ethoxyacetylene. The preferred condensing agent is dicyclohexylcarbodiimide. Examples of said solvents which may be employed are dichloromethane, chloroform, tetrahydrofuran, ethyl ether and benzene. While the reaction may be carried out at a temperature of from about −10 to 50°C. with satisfactory results, it is preferred to employ a temperature of from about 0 to 30°C. At this temperature the reaction is ordinarily complete in a few hours. The product of formula (XIII) is isolated, for example, by filtering to remove insoluble material and evaporation of solvent. The resulting product is ordinarily of sufficient purity for use in the next step.

The intermediate of formula (XIII) is then reacted with lithium aluminum hydride as described above in the preparation of 2-methyl compounds of formula (XI). The product of formula (VI) is isolated also as described above and purified, for example, by column chromatography on silica gel.

An alternate method for providing the 4a,9b-*trans*-compounds of formula (VI) in admixture with the corresponding dehydrated compounds of formula (VII) is illustrated as follows:

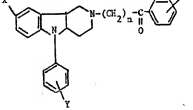


In which X, Y, Z, n and m are as previously defined. The reaction with borane in ether solvent preferably in tetrahydrofuran and subsequent treatment with acid is carried out under the conditions described above for preparation of the 2-benzyl compounds of formula (IX). The products (VI) and (VII) are separated, for example by column chromatography on silica gel.

The relative amounts of products (VI) nd (VII) will vary depending upon the amount of acid, for example, hydrochloric acid, and the time of heating at reflux after the reduction with $BH_3 \cdot THF$ has taken place. Higher amounts of acid and longer reflux times favor the dehydrated product of formula (VII); while lower amounts of acid and shorter reflux periods favor the formation of the product (VI).

The compounds of formula (VI) may also serve as precursors of the free bases of formula(X). This is carried out employing, for example, ethyl chloroformate followed by alkaline hydrolysis as described above for the debenzylation of the compounds of formula (IX) wherein $R_2$ is benzyl, to obtain the free bases of formula (X).

Oxidation of the compounds of formula (VI) employing reagents and conditions which are known to selectively convert secondary alcohols to the corresponding ketones, provides the novel products of formula



wherein X, Y, Z and n are as previously defined. Examples of such oxidizing agents which may be employed in this reaction are potassium permanganate, potassium dichromate and chromium trioxide and the preferred reagent is chromium trioxide in the presence of pyridine. In carrying out this reaction with the preferred reagent, the starting alcohol of formula (VI) in a reaction-inert solvent, for example, dichloromethane, chloroform or benzene, is added to a mixture containing up to a ten molar excess of chromium trioxide and a similarly large molar excess of pyridine and the mixture stirred, ordinarily at room temperature, until the reaction is substantially complete. Ordinarily, from about 15 minutes to one hour will suffice. The product is isolated, for example, by removal of insoluble material by filtration, extracting the filtrate with a dilute aqueous alkali such as sodium hydroxide solution, drying the organic layer and evaporating to dryness. The residual product may be further purified, if desired, for example, by column chromatography.

2-Benzyl-5-phenyl-1,2,3,4-tetrahydro-γ-carboline is obtained by the Fischer indole synthesis employing N,N-diphenylhydrazine and N-benzyl-4-piperidone. The mono or difluoro-substituted starting tetrahydro-γ-carbolines of formula (VIII) wherein at least one of X or Y is fluoro and $R_2$ is benzyl, are prepared from the corresponding compounds of

formula (VIII) wherein $R_2$ is hydrogen by reaction with a benzyl halide such as benzyl bromide, in equimolar amounts. The requisite compounds of formula (VIII, $R_2$ = H) are prepared as described in British Patent Specification No. 1476087. The starting tetrahydro-γ-carbolines (V) are described in the same reference.

The other starting materials are either commercially available, their preparation is explicitly reported in the chemical literature or they can be prepared by methods known to those skilled in the art. For example, the phenylhydrazines are commercially available or are synthesized by reduction of the phenyldiazonium salt as reviewed by Wagner and Zook in "Synthetic Organic Chemistry", John Wiley & Sons, New York, N. Y., 1956, Chapter 26; the 1-substituted-4-piperidones are commercial reagents or prepared by the method of McElvain and Rorig, *J. Am. Chem. Soc., 70*, 1826 (1948); the requisite 3-benzoylpropionic acids and 4-benzoylbutyric acids are either commercially available or prepared by modification of the procedure of "Organic Synthesis", Coll. Vol. 2, John Wiley and Sons, New York, N. Y., 1943, P. 81.

As has been previously mentioned, the basic compounds of the present invention can form acid addition salts. Said basic compounds are converted to their acid addition salts by interaction of the base with an acid either in an aqueous or nonaqueous medium. In a similar manner, treatment of the acid addition salts with an equivalent amount of an aqueous base solution, e.g., alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates or with an equivalent amount of a metal cation which forms an insoluble precipitate with the acid anion, results in the regeneration of the free base form. The bases thus regenerated may be reconverted to the same or a different acid addtion salt.

In the utilization of the chemotherapeutic activity of said salts of the compounds of the present invenion, it is preferred, of course, to use pharmaceutically acceptable salts. Although water-insolubility, high toxicity, or lack of crystalline nature may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water insoluble or toxic salts can be converted to the corresponding pharmaceutical acceptable bases by decomposition of the salt as described above, or alternately, they can be converted to any desired pharmaceutically acceptable acid addition salt.

Examples of acids which provide pharmaceutically acceptable anions are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, sulfurous, phosphoric, acetic, lactic, citric, tartaric, succinic, maleic and gluconic acids.

As previously indicated, the compounds of the present invention are readily adapted to therapeutic use as tranquilizing agents in mammals.

The tranquilizing agents of the present invention are characterized by relief of such schizophrenic manifestations in humans as hallucinations, hostility, suspiciousness, emotional or social withdrawal, anxiety, agitation and tension. Standard procedures of detecting and comparing tranquilizing activity of compounds in this series and for which there is an excellent correlation with human efficacy is the antagonism of amphetamine-induced symptoms in rats test, as taught by A. Weissman, *et al., J. Pharmacol Exp.* Ther., 151, 339 (1966) and by Quinton, *et al., Nature, 200*, 178 (1963).

The γ-carbolines and the pharmaceutically acceptable salts thereof, which are useful as tranquilizers, can be administered either as individual therapeutic agents or as mixtures of therapeutic agents. They may be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they can be administered orally in the form of tablets or capsules containing such excipients as starch, milk sugar, or certain types of clay. They can be administered in the form of elixirs or oral suspensions with the active ingredients combined with emultsifying and/or suspending agents. They may be injected parenterally, and for this use they, or appropriate derivatives, may be prepared in the form of sterile aqueous solutions. Such aqueous solutions should be suitable buffered, if necessary, and should contain other solutes such as saline or glucose to render them isotonic.

Although use of compounds of the present invention is directed toward the treatment of mammals in general, the preferred subject is humans. Obviously, the physician will ultimately determine the dosage which will be most suitable for a particular individual, and it will vary with age, weight and response of the particular patient, as well as with the nature and extent of the symptoms and the pharmacodynamic characteristics of the particular agent to be administered. Generally, small doses will be administered initially, with a gradual increase in the dosage until the optimum level is determined. It will often be found that when the composition is administered orally, larger quantities of the active ingredient will be required to produce the same level as produced by a smaller quantity administered parenterally.

Having full regard for the foregoing factors, it is considered that a daily dosage of the

compounds of the instant invention in humans of approximately 0.5 to 100 mg., with a preferred range of 1 to 25 mg., will tranquilize effectively. In those individuals in which the compounds of the present invention have a prolonged effect, the dose can be 5 to 125 mg. a week, administered in one or two divided doses. The values are illustrative, and there may, of course, be individual cases where higher or lower dose ranges are merited.

The following Examples are provided solely for the purpose of illustration and are not to be construed as limitations of the invention, many variations of which are possible without departing from the spirit or scope thereof. Examples 1, 2 5 and 6 illustrate the preparation of starting materials which are used in subsequent Examples 10 and 11.

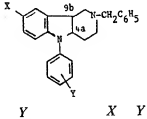
EXAMPLE 1

*d1-trans-2-benzyl-2,3,4,4a,5,9b-hexahydro-5-phenyl-1H-pyrido-[4,3-b]indole Hydrochloride*

To a solution of 0.140 moles of borane in 150 ml. of tetrahydrofuran stirred at 0°C in a three-necked round bottom flask fitted with magnetic stirred, thermometer, condenser and addition funnel, and maintained under a nitrogen atmosphere, was added a solution of 23.9 g. (0.071 mole) of 2-benzyl-5-phenyl-1,2,3,4-tetrahydropyrido[4,3-b]indole in 460 ml. of dry tetrahydrofuran. The addition was carried out at such a rate as to maintain the reaction temperature below 9°C. When the addition was completed the resulting mixture was heated to reflux and maintained at this temperature for one hour. The solvent was then evaporated *in vacuo* to afford a white solid mass which was suspended in 40 ml. of dry tetrahydrofuran and heated, slowly at first, with 180 ml. of a 1:1 by volume mixture of acetic acid and 5*N* hydrochloric acid. The resulting suspension was heated at reflux for one hour, then cooled. Evaporation of tetrahydrofuran and part of the acetic acid resulted in precipitaton of a white solid which was separated by filtration and washed with water. The solid was resuspended in tetrahydrofuran, filtered, washed with ethyl ether and air dried to afford 16.7 g. (63%) of the desired *trans*-isomer. M. P. 256-260°C.

Evaporation of the mother liquor gave an additional 7.2 g. of product contaminated with a small amount of the *cis*-isomer.

When the above procedure is repeated, but employing the appropriately substituted 2-benzyl-5-phenyl-1,2,3,4-tetrahydropyrido[4,3-b]indole as starting material, the following 4a,9b-*trans*-compounds are obtained in like manner as their hydrochloride salts.




| X | Y | X | Y |
|---|---|---|---|
| H | *p*-fluoro | H | *o*-fluoro |
| F | H | F | *m*-fluoro |
| F | *p*-fluoro | F | *o*-fluoro |

EXAMPLE 2

*d1-trans-5-Phenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole*

A suspension of 4.17 g. *d1-trans*-2-benzyl-5-phenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride in 150 ml. of absolute ethanol was hydrogenated at 50 p.s.i. and 60-70°C. using 1.0 g. of 10% Pd/C catalyst, over a two-hour period. The catalyst was removed by filtration and to the filtrate was added sufficient ethyl ether to precipitate the hydrochloride of the desired product, 2.76 g. (87%), M.P. 235-237°C.

The hydrochloride salt was converted to free base by partitioning between ether and dilute sodium hydroxide solution. The ether layer was dried over sodium sulfate and evaporated to afford the title compound (97% yield), M.P. 74-76°C.

EXAMPLE 3

*d1-trans-8-Fluoro-5-p-fluorophenyl)-2-[4-hydroxy-4-(p-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride and*
*d1-trans-8-Fluoro-5-(p-fluorophenyl)-2-[4-(p-fluorophenyl)-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride*

In a 1000 ml. reaction vessel equipped with magnetic stirred, dropping funnel and maintained under a nitrogent atmosphere were placed 177 ml. of 0.94 molar borane in tetrahydrofuran. The solution was cooled in an ice bath and to the cold solution was added over 30 minutes a solution of 25 g. (0.0555 mole) of 8-fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,5-tetrahydropyrido[4,3-b]indole in 295 ml. of tetrahydrofuran. The resulting mixture was stirred at ambient temperature for 20 minutes, then heated at reflux for two hours. The reaction mixture was cooled and concentrated *in vacuo* to obtain a liquid residue. To this was added a mixture of 50 ml. each of acetic acid and 5*N* hydrochloric acid whereupon vigorous gas evolution took place. The mixture was heated at reflux for one hour, cooled to room temperature and filtered. The filtrate was cooled in ice and made alkaline by addition of 50% (w/w) sodium hydroxide solution. The basic mixture was extracted twice with 150 ml. portions of chloroform, the combined organic layers dried over magnesium sulfate and evaporated to dryness *in vacuo* to obtain a yellow foamed solid, 25 g. Silica gel thin-layer chromatography, employing a 1:1 by volume hexane/ethyl acetate solvent system, revealed two products. The foamed solid was chromatographed on a column of silica gel, eluting with 1:1 by volume hexane/ethyl acetate and monitoring the fraction by TLC. The fractions containing only the faster moving product, i.e. 8-fluoro-5-*p*-fluorophenyl)-2-[4-(*p*-fluorophenyl)-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole were evaporated to dryness taken up in acetone and converted to the hydrochloride salt by addition of anhydrous hydrogen chloride in acetone, the resulting white solid was collected by filtration and dried to obtain 1.5 g. of the 3-butenyl compound, M.P. 270-273°C.

The fractions containing only the slower moving 8-fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole were concentrated, taken up in ethyl ether and converted to hydrochloride salt by addition of anhydrous hydrogen chloride to obtain 10.8 g. of this product, M.P. 241-245°C.

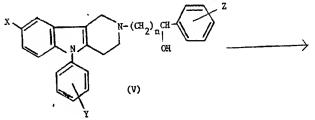
The proportion of the faster moving 3-butenyl compound is increased, up to 100%, by suitable increase in the acidiy and period of heating at reflux in the acetic/hydrochloric acid mixture.

EXAMPLE 3A

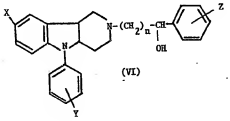
When the procedure of Example 3 was repeated, but starting with 8-fluoro-5-(*o*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,5-tetrahydropyrido[4.3-b]indole, the faster moving component from silica gel chromatography was identified as *trans*-8-fluoro-5-(*o*-fluorophenyl)-2-[4-(*p*-fluorophenyl)-3-butenyl]l-2,3,4,4a,9b-hexahydro-1H-pyrido[4,3-b]indole, M.P. 141-142°C. The slower moving component was identified as *trans*-8-fluoro-5-(*o*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]-indole, M.P. 195-197°C.

EXAMPLE 4

Employing the appropriate compounds of formula (V) as starting materials in the procedure of Example 3, the indicated 4a, 9b-*trans*-products of formulae (VI) and (VII) were obtained and separated in each case. In the products of formula (VII) m = n−1.

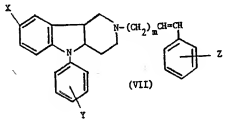



(V)



(VI)

+



(VII)

| *n* | *X* | *Y* | *Z* |
|---|---|---|---|
| 3 | F | *p*-fluoro | *m*-fluoro |
| 3 | F | *p*-fluoro | H |
| 3 | H | *p*-fluoro | *p*-methoxy |
| 3 | F | H | *o*-methoxy |
| 3 | H | H | *p*-fluoro |
| 4 | F | *p*-fluoro | *p*-fluoro |
| 4 | F | *p*-fluoro | *p*-methoxy |
| 4 | F | *p*-fluoro | H |
| 4 | F | H | *o*-fluoro |
| 4 | F | H | *m*-methoxy |
| 4 | H | *p*-fluoro | *p*-fluoro |
| 4 | H | *p*-fluoro | H |
| 4 | H | H | H |
| 4 | H | *o*-fluoro | *p*-fluoro |
| 3 | H | *o*-fluoro | *p*-fluoro |
| 3 | H | *m*-fluoro | *m*-fluoro |
| 3 | F | *o*-fluoro | *p*-methoxy |
| 3 | H | *p*-fluoro | H |
| 4 | F | *o*-fluoro | *o*-fluoro |
| 4 | F | *m*-fluoro | *p*-methoxy |

EXAMPLE 5

*dl-trans-8-Fluoro-5-(p-fluorophenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole*

A. To a solution of 5.6 g. (12.4 mmole) of *dl-trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole in 40 ml. of toluene was added 5.3 ml. (55.7 mmole) of ethyl chloroformate. The resulting mixture refluxed overnight then evaporated to dryness to obtain a residual gum. To the gum was added 200 ml. of a 9:1 by volume mixture of ethanol/water. After the gum was dissolved, 15 g. of potassium hydroxide was added and the resulting mixture refluxed overnight. The solvent was evaporated *in vacuo* and the residue partitioned between water and chloroform. The organic extracts were washed with water, dried over sodium sulfate and evaporated to dryness. The residual oil was taken up in ethyl acetate and passed through a silica gel column eluting first with ethyl acetate to remove by-products then eluting the desired product with 1:1 by volume ethyl acetate/methanol. The fractions containing the title compound were combined and evaporated to dryness to obtain 1.5 g. (43%) of yellow gum which crystallized upon standing, M.P. 115°-117°C.

B. Alternately, *dl-trans*-2-benzyl-8-fluoro-5-(*p*-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride is refluxed in the presence of excess ethyl chloroformate or the corresponding methyl, isopropyl or *n*-butyl chloroformate esters, then hydrolyzed and worked up by the procedure described above to obtain the title compound.

EXAMPLE 6

Employing the appropriate starting material in each case and employing the procedures of Example 5A or 5B, the following products are similarly obtained:

*dl-trans*-5-(*p*-fluorophenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]-indole,
*dl-trans*-8-fluoro-5-phenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]-indole,
*dl-trans*-5-(*o*-fluorophenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]-indole,
*dl-trans*-l5-*o*-fluorophenyl)-8-fluoro-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*dl-trans*-5-(*m*-fluorophenyl)-8-fluoro-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole,
*dl-trans*-5-(*m*-fluorophenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]-indole.

EXAMPLE 7

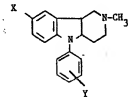
*d1-trans-8-Fluoro-5-(p-fluorophenyl)-2-methyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole Hydrochloride*

A. In a 25 ml. flask fitted with stirrer, dropping funnel and nitrogen inlet were placed 573 mg. (2.0 mmole) of 8-fluoro-5-(*p*-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole, 8 ml. of dichloromethane and 0.323 ml. (4 mmole) of dry pyridine. To the resulting solution at room temperature was added dropwise a solution of 0.219 ml. (2.3 mmole) of ethyl chloroformate. After the addition was completed the mixture was stirred for one hour. The mixture was then evaporated *in vacuo* to afford a residual gum. This was partitioned between 10 ml. of 10% hydrochloric acid and 25 ml. of ether. The organic layer was washed with water (10 ml.), dried over magnesium sulfate and evaporated to dryness to afford 707 mg. of 8-fluoro-5-(*p*-fluorophenyl)-2-ethoxycarbonyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole which was used in the next step.

B. In a 100 ml. flask equipped with magnetic stirrer, dropping funnel and nitrogen inlet tube were placed 10 ml. of ethyl ether and 524 mg. (13.8 mmole) of lithium aluminum hydride. The suspension was cooled by means of an ice-bath. After stirring under a nitrogen atmosphere for 5 minutes a solution of the product from part A, above, 707 mg. (1.97 mmole) in 5 ml. of ether was added dropwise over a 5 minute period. The resulting mixture was then stirred at room temperature for one hour, after which 3 g. of anhydrous sodium sulfate was added, followed by slow addition of about 1 ml. of water. After stirring for 30 minutes the resulting mixture was filtered and the collected white solid washed with ether. The filtrate was evaporated to dryness, redissolved in ether and a saturated solution of anhydrous hydrogen chloride in ether was added until precipitation was complete. The resulting precipitate was recovered by filtration to obtain 481 mg. of the title compound. Infrared spectrum (KBr), μ: 2.92, 3.42, 3.02-4.10, 6.64, 6.80, 7.97, 8.23, 8.55, 8.73, 11.94, 12.35, 12.90; Mass spectrum, m/e: 300, 256, 240, 242, 229, 201, 146, 109, 95, 74, 58 (109%); $^1$H NMR ($CDCl_3$), δ: 1.84-2.50 (4H, m), 2.52 (3H, s), 2.98-3.26 (3H, m), 3.46-3.64 (1H, m), 6.50-7.46 (7H, m).

EXAMPLE 8

When the products provided in Example 6 are reacted with ethyl chloroformate in the presence of pyridine and solvent as described in Example 7A and the resulting 2-ethoxycarbonyl derivative reduced as described in Example 7B, the following racemic 4a, 9b-*trans* compounds ae similarly obtained:



| X | Y |
|---|---|
| H | *p*-fluoro |
| F | H |
| H | *o*-fluoro |
| F | *o*-fluoro |
| F | *m*-fluoro |
| H | *m*-fluoro |

EXAMPLE 9

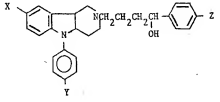
*d1-trans-2-(4-Hydroxy-4-phenylbutyl)-5-phenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole Hydrochloride*

A. To the suspension arising from the admixture of 865 mg. (4.20 mmole) of dicyclohexylcarbodiimide and 748 mg. (4.20 mmole) of 3-benzoylpropionic acid in 30 ml. of dichloromethane at 0°C. was added 1.0 g. (4.0 mmol) of *d1-trans*-5-phenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole in 10 ml. of the same solvent. The resulting mixture was stirred and allowed to warm to room temperature over 2 hours. After cooling again to 0°C. the reaction mixture was filtered, washed with dichloromethane and the filtrates evaporated to obtain a residue of *d1-trans*-2-[(3-benzoyl)propionyl]-5-phenyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole which was used without purification in the next step.

B. The residue from above was dissolved in 50 ml. of tetrahydrofuran and heated to reflux. A filtered solution of lithium aluminum hydride in the same solvent was added until gas evolution ceased (molar excess), and the resulting mixture was stirred at reflux for 5-10 minutes, then cooled. Anhydrous powdered sodium sulfate, 17 g., was added followed by 0.5 ml. of water. The resulting mixture was stirred at room temperature for 30 minutes, filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was chormatographed on a column containing 80 g. of silica gel, eluting with 4:1 (v/v) ethyl acetate/methanol to afford the free base of the title compound after evaporation of solvent. The free base was converted to the hydrochloride salt by dissolving it in ether, adding a saturated solution of anhydrous hydrogen chloride in ether until precipitation was complete, filtering and drying to afford 1.04 g., M.P. 222-224°C. Infrared spectrum (KBr), μ: 2.97, 3.43, 4.00 (broad), 6.25, 6.68, 6.88, 7.51, 7.96, 8.18, 8.45, 9.82; Mass spectrum M/e, 398, 292, 263, 249, 220, 207, 192 (100%); UV(methanol) $\lambda_{max}$ 245 ($\varepsilon = 0.653 \times 10^4$), 270 ($\varepsilon = 0.914 \times 10^3$).

EXAMPLE 10

Employing the appropriate starting material in each case selected from the free bases provided in Examples 2 and 5 and the appropriate 3-benzoyl-propionic acid, the following *d1-trans*-compounds were prepared by the procedure of Example 9. Products were isolated as the hydrochloride salts except as indicated.



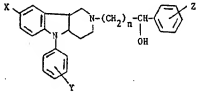
| X | Y | Z | M.P., °C. | Yield, % |
|---|---|---|---|---|
| F | F | H | 220-223 | 18 |
| H | H | F | 239-245 | 39 |
| H | H | $CH_3O$ | amorphous solid (a) | 54 |
| F | F | $CH_3O$ | 45-48.5 (b) | 31 |

(a) Mass spectrum, M/e: 428, 411, 263 (100%), 220, 206, 204: Infrared spectrum (KBr), μ: 2.98, 3.42, 4.07 (broad), 6.20, 6.26, 6.70, 6.88, 8.04, 8.54, 9.77, 12.05.

(b) Melting point and yield data are for the free base.

EXAMPLE 11

Starting with the appropriate *dl-trans*-hexahydro-1H-pyrido[4,3-b]-indole selected from the products of Examples 2, 5 and 6 and the appropriately substituted 3-benzoylpropionic or 4-benzoylbutyric acid, the following compounds are obtained by the method of Example 9.




| n | X | Y | Z |
|---|---|---|---|
| 3 | F | *p*-fluoro | *m*-fluoro |
| 3 | F | *p*-fluoro | *o*-methoxy |
| 3 | F | H | *p*-fluoro |
| 3 | H | *p*-fluoro | *p*-methoxy |
| 3 | H | *o*-fluoro | *m*-methoxy |
| 3 | F | H | H |
| 3 | H | *m*-fluoro | H |
| 3 | H | H | *m*-fluoro |
| 4 | F | *p*-fluoro | *p*-fluoro |
| 4 | F | *p*-fluoro | *p*-methoxy |
| 4 | F | *o*-fluoro | H |
| 4 | F | H | H |
| 4 | F | H | *m*-methoxy |
| 4 | H | *p*-fluoro | H |
| 4 | H | *m*-fluoro | *o*-fluoro |

| | | | | |
|---|---|---|---|---|
| 4 | H | *o*-fluoro | *p*-methoxy | |
| 4 | H | H | *o*-methoxy | |
| 3 | H | *p*-fluoro | *p*-fluoro | |
| 3 | H | *o*-fluoro | *o*-fluoro | |
| 3 | F | *m*-fluoro | *p*-fluoro | |
| 3 | H | *m*-fluoro | *p*-fluoro | |

EXAMPLE 12

*d1-trans-5-Phenyl-2-[3-(p-fluorobenzoyl)propyl]-3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole Hydrochloride*

In a 25 ml. reaction vessel equipped with magnetic stirrer and maintained under a nitrogen atmosphere were placed 0.828 ml. (8.0 mg., 10.3 mmole) of dry pyridine and 10 ml. of dichloromethane. To the solution was added 517 mg. (5.17 mmole) of chromium trioxide and the resulting dark red suspension stirred for 15 minutes at room temperature. A solution of 359 mg. (0.862 mmole) of *d1-trans*-5-phenyl-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole free base is 5 ml. of dichloromethane was added in one portion. The reaction mixture quickly changed to a brown suspension. This was stirred at ambient temperature for 30 minutes. The insoluble material was removed by filtration, washed with dichloromethane and the combined filtrate and washings were extracted with 20 ml. of 10% sodium hydroxide solution. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford a gum. The gum was purified by column chromatography on silica gel, eluting with 1:1 by volume hexane/ethyl acetate. The fractions containing the desired product were combined, evaporated to a yellow gum, the gum taken up in ethyl ether and treated with anhydrous hydrogen chloride. The resulting supension was evaporated to dryness, slurried with 3 ml. of cold dichloromethane. A colorless solid formed which was collected by filtration and dried to afford 20 mg. of the title compound, M.P. 244-246.5°C.

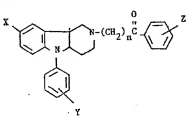
EXAMPLE 13

*d1-trans-8-Fluoro-5-(p-fluorophenyl)-2-[3-(p-fluorobenzoyl)propyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole Hydrochloride*

To a 100 ml. flask containing 20 ml. of dichloromethane and 1.76 ml. (21.9 mmole) of pyridine was added 1.09 g. of chromium trioxide and the resulting dark suspension was stirred at ambient temperature for 15 minutes. Then was added in one portion a solution of 824 mg. (1.82 mmole) of *d1-trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole free base (obtained from the hydrochloride salt by making an aqueous solution alkaline with sodium hydroxide, extracting with dichloromethane and evaporating the extracts to dryness) in 10 ml. of dichloromethane. The resulting red-brown suspension was stirred at ambient temperature for one hour and worked-up by the same procedure employed in Example 12 to obtain 25 mg. of the desired product, M.P. 260-263°C.

EXAMPLE 14

Employing the appropriate starting material selected from the products obtained in Example 9, 10 and 11 and oxidizing by the procedure of Example 12 affords the following 4a, 9b-*trans* compounds:



| n | X | Y | Z |
|---|---|---|---|
| 3 | F | *p*-fluoro | H |
| 3 | H | H | *p*-fluoro |
| 3 | H | H | *p*-methoxy |
| 3 | F | *p*-fluoro | *p*-methoxy |
| 3 | H | *p*-fluoro | *p*-methoxy |
| 3 | H | *o*-fluoro | *m*-methoxy |
| 3 | F | H | *p*-fluoro |
| 3 | F | H | H |
| 3 | H | H | H |
| 3 | F | *p*-fluoro | *m*-fluoro |
| 3 | H | *m*-fluoro | H |
| 4 | F | *p*-fluoro | *p*-fluoro |
| 4 | F | *p*-fluoro | *p*-methoxy |
| 4 | F | *o*-fluoro | H |
| 4 | F | H | H |
| 4 | F | H | *m*-methoxy |
| 4 | H | *p*-fluoro | H |
| 4 | H | *m*-fluoro | *o*-fluoro |
| 4 | H | *o*-fluoro | *p*-methoxy |
| 4 | H | H | *o*-methoxy |
| 3 | H | *p*-fluoro | *p*-fluoro |
| 3 | H | *o*-fluoro | *o*-flouro |
| 3 | F | *m*-fluoro | *p*-fluoro |
| 3 | H | *m*-fluoro | *p*-fluoro |

EXAMPLE 15

*d1-trans-8-Fluoro-5-(p-fluorophenyl)-2-[4-hydroxy-4-(p-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole acetate*

Five grams of *d1-trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride in 75 ml. of water is treated with 3 ml. of water containing 1.0 g. of sodium hydroxide, and the liberated free base extracted into 150 ml. of diethyl ether. The ether layer is separated, dried over magnesium sulfate and treated with 1 ml. of glacial acetic acid. The organic solvent and excess acetic acid are removed under reduced pressure and the residue triturated with hexane and filtered.

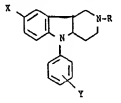
In a similar manner, other acid addition salts, especially those which are pharmaceutically acceptable, can be prepared.

EXAMPLE 16

*Test procedures and results*

The effects of the compounds of the present invention on prominent amphetamine-induced symptoms were studied in rats by a rating scale modeled after the one reported by Quinton and Halliwell, and Weissman. Groups of five rats were placed in a covered plastic cage measuring approximately 26 cm. × 42 cm. × 16 cm. After a brief period of acclimation in the cage, the rats in each group were treated subcutaneously (s.c.) with the test compound. They were then treated 1, 2 and 24 hrs. later with *d*-amphetamine sulfate, 5 mg./kg. intraperitoneally (i.p.). One hour after amphetamine was given each rat was observed for the characteristic amphetamine behavior of moving around the cage. On the basis of dose-response data after amphetamine it was possible to determine the effective dose of the compound necessary to antagonize or block the characteristic amphetamine behavior of cage movement for fifty percent of the rats tested ($ED_{50}$). The time of rating chosen coincides with the peak action of amphetamine which is 60-80 min. after treatment with this agent.

Employing the above-described procedure, the following 4a,9b-*trans* compounds were tested for their ability to block the behavior effects of amphetamine, the results being reported as the $ED_{50}$ in mg./kg. at the indicated times.



(Example 16 Continued)

| X | Y | R | $ED_{50}$ (mg./kg.) | | |
|---|---|---|---|---|---|
| | | | 1 Hr. | 2 Hrs. | 24 Hrs. |
| H | H | $C_6H_5CH(OH)-(CH_2)_3-$ | 0.032-0.1 | 0.032-0.1 | 0.1-0.32 |
| H[a] | H | $p$-$FC_6H_4CH(OH)-(CH_2)_3-$ | 0.1-0.32 | 0.1-0.32 | 0.1-0.32 |
| H | H | $p$-$CH_3OC_6H_4CH(OH)-(CH_2)_3-$ | 0.1-0.32 | 0.1-0.32 | ~1.0 |
| H | H | $p$-$FC_6H_4C(=O)-(CH_2)_3-$ | ~0.32 | 0.1-0.32 | ~0.32 |
| F | $p$-fluoro | $CH_3-$ | ~0.1 | 0.1-0.32 | >3.2 |
| F | $p$-fluoro | $C_6H_5CH(OH)-(CH_2)_3-$ | 0.1-0.32 | 0.1-0.32 | <0.32 |
| F | $o$-fluoro | $p$-$FC_6H_4CH(OH)-(CH_2)_3-$ | <0.32 | <0.32 | <0.32 |
| F | $p$-fluoro | $p$-$FC_6H_4CH(OH)-(CH_2)_3$ | 0.032-0.1 | 0.032-0.1 | 0.032-0.1 |
| F[b] | $p$-fluoro | $p$-$FC_6H_4CH=CH-(CH_2)_2-$ | 0.32-1.0 | <0.32 | <0.32 |
| F | $o$-fluoro | $p$-$FC_6H_4CH=CH-(CH_2)_2-$ | 10 | 3.2-10 | 3.2-10 |
| F | $p$-fluoro | $p$-$CH_3OC_6H_4CH=CH-(CH_2)_2-$ | 1-3.2 | <1 | <1 |

(Example 16 Continued)

| | | | | | |
|---|---|---|---|---|---|
| F | *p*-fluoro | *p*-$CH_3OC_6H_4CH(OH)-(CH_2)_2-$ | 0.1-0.32 | <0.1 | <0.32 |
| F | *p*-fluoro | *p*-$FC_6H_4C(=O)-(CH_2)_3-$ | <1.0 | <1.0 | <1.0 |

| | $ED_{50}$ (mg./kg.) | | |
|---|---|---|---|
| 8-Fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)-butyl]-1,2,3,4-tetrahydro-carboline[e] | 0.1-0.32 | 0.1-0.32 | 0.32-1.0 |
| Navane[f], po | 0.32-1.0 | >10 | >32 |

*Footnotes*

(a) The corresponding 4a,9b-*cis* analog was found to have an $ED_{50}$ −56 mg./kg. at 1 hour.

(b) $ED_{50}$ at 48 hours, <0.32: 72 hours, <0.32

(e) U.K. Patent Specification No. 1476087 - included for comparison

(f) *cis*-9-[3-(4-Methyl-1-piperazinyl)propylidene]-2-(dimethylsulfonamido)thioxanthene, U.S. 3,310,553 - included for comparison

EXAMPLE 17

*Tablets*

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated:

| | |
|---|---|
| Sucrose, U.S.P | 80.3 |
| Tapioca starch | 13.2 |
| Magnesium stearate | 6.5 |

Into this tablet base there is blended sufficient *trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-(*p*-fluorophenyl)-4-hydroxybutyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride to provide tablets containing 1.0, 2.5, 5.0 and 10 mg. of active ingredient per tablet. The compositions are each compressed into tablets, each weighing 360 mg., by conventional means.

EXAMPLE 18

*Capsules*

A blend is prepared containing the following ingredients:

| | |
|---|---|
| Calcium carbonate, U.S.P. | 17.6 |
| Dicalcium phosphate | 18.8 |
| Magnesium trisilicate, U.S.P. | 5.2 |
| Lactose, U.S.P. | 5.2 |
| Potato starch | 5.2 |
| Magnesium stearate | 0.8 |

To this blend is added a second portion of magnesium stearate (0.35 g.) and sufficient *trans*-5-phenyl-2-(4-hydroxy-4-phenylbutyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole hydrochloride to provide capsules containing 1.0, 2.5, 5.0 and 10 mg. of active ingredient per capsule. The compositions are filled into conventional hard gelatin capsules in the amount of 350 mg. per capsule.

EXAMPLE 19

*Suspension*

A suspension of *trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-methoxyphenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido(4,3-b]indole acetate is prepared with the following composition:

| | | |
|---|---|---|
| Effective ingredient | g. | 25.00 |
| 70% aqueous sorbitol | g. | 741.29 |
| Glycerine, U.S.P. | g. | 185.35 |
| Gum acacia (10% solution) | ml. | 100.00 |
| Polyvinylpyrrolidone | g. | 0.50 |

Distilled water, sufficient to make 1 liter.

To this suspension, various sweeteners and flavorants are added to improve the palatability of the suspension. The suspension contains approximately 25 mg. of effective agent per milliliter.

EXAMPLE 20

Sesame oil is sterilized by heating to 120°C. for 2 hrs. To this oil, a sufficient quantity of pulverized *trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-(*p*-fluorophenyl)-4-hydroxybutyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]-indole hydrochloride to make a 0.025% suspen-

sion by weight. The solid is thoroughly dispersed in the oil by use of a colloid mill. It is then filtered through a 100-250 mesh screen and poured into sterile vials and sealed.

PREPARATION A

*2-Benzyl-5-phenyl-1,2,3,4,-tetrahydro-γ-carboline*

Crude N,N-diphenylhydrazine, 100 g. was made alkaline with aqueous potassium hydroxide and the mixture extracted with ethyl acetate. The organic layer was distilled to afford 39.7 g. (0.216 mole) of N,N-diphenylhydrazine, free base, B.P. 130-135°C. at 1.1 mm. Hg. This was dissolved in 500 ml. of absolute ethanol and 40.8 g. (0.216 mole) of N-benzyl-4-piperidone in 500 ml. of absolute ethanol was added. The resulting mixture was heated to 65°C. and dry hydrogen chloride gas was added to acidify the mixture which was then heated at reflux for five hours. After standing overnight at room temperature the solvent was evaporated and the residue made alkaline with sodium hydroxide solution, extracted with chloroform, the extracts dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in ethyl ether, filtered and the filtrate acidified with an ethereal solution of hydrogen chloride to precipitate the crude hydrochloride salt. The salt was converted to the free base by partitioning between aqueous sodium hydroxide and ethyl acetate. The organic layers were dried, concentrated to a small volume and chromatographed on 300 g. of silica gel eluting with 5:1 hexane/ethyl acetate (by volume) to afford 12.0 g. (33%) of the desired product, M.P. 150-155°C.

PREPARATION B

*8-Fluoro-5-(p-fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline*

I. *8-fluoro-2-carbethoxy-1,2,3,4-tetrahydro-γ-carboline*

A mixture of 15.9 g. (0.093 mole) of N-carbethoxy-4-piperidone and 15.1 g. (0.093 mole) of *p*-fluorophenylhydrazine hydrochloride in 150 ml. of ethanol is heated to reflux for 2 hrs. The reddish reaction mixture is cooled and filtered, and the collected solids washed with a small amount of cold 95% ethanol, 21.3 g. (88% yield), m.p. 169-170°C. The analytical sample is recrystallized from ethanol-water, m.p. 169-170°C.

Anal. Calc'd for $C_{14}H_{15}O_2N_2F$: C, 64.1; H, 5.8; N, 10.7.

Found: C, 63.8; H, 5.8; N, 10.6.

II. *8-fluoro-5-(p-fluorophenyl)-2-carbethoxy-1,2,3,4-tetrahydro-γ-carboline*

To 30 ml. of N-methyl-2-pyrrolidone is added 3.45 g. (0.013 mole) of 8-fluoro-2-carbethoxy-1,2,3,4-tetrahydro-γ-carboline, 7.8 g. (0.045 mole) of *p*-fluorobromobenzene, 4.14. g. (0.014 mole) of cuprous bromide and 1.5 g. (0.014 mole) of sodium carbonate, and the resulting mixture heated in an oil bath at 200°C. for 6 hrs. The mixture is allowed to cool to room temperature overnight, and is then decanted into 300 ml. of water containing 60 ml. of ethylene diamine. Benzene (200 ml.) is added and the two-phase system is filtered through a supercel(registered trade mark) pad. The filtrate is subsequently extracted several times with a total of 700 ml. of benzene. The extracts are combined, washed successively with water and a saturated brine solution and dried over anhydrous sodium sulfate. Removal of the solvent provides the crude product as a dark, residual oil.

The crude product in benzene is chromatographed on a silica gel column using 10% ethyl acetate-benzene as the eluate. Fractions 1 through 16, comprised of 10-25 ml. each, and containing *p*-fluorobromobenzene, are collected and discarded. Fractions 16 to 38 are combined and concentrated *in vacuo* to an oil which solidifies on standing at 5°C overnight. The product, 3.5 g. (76% yield) is triturated with pentane and filtered. The analytical sample is recrystallized from pentane, m.p. 118-120°C.

Anal. Calc'd for $C_{20}H_{18}O_2N_2F_2$: C, 67.4; H, 5.1; N, 7.9.

Found: C, 67.4; H, 5.2; N, 7.8.

III. *8-fluoro-5-(p-fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline*

A suspension of 3.56 g. (0.01 mole) of 8-fluoro-5-(*p*-fluorophenyl)-2-carbethoxy-1.2.3.4-tetrahydro-γ-carboline and 8.2 g. (0.146 mole) of potassium hydroxide in 53 ml. of ethanol containing 5 ml. of water is heated to reflux overnight. An additional 3.0 g. of potassium hydroxide is added and the heating continued for 23 hrs. The brownish solution is cooled, concentrated *in vacuo* to dryness and partitioned between water and diethyl ether. The aqueous layer is further extracted with ether, and the ether layers combined, washed with a saturated brine solution and dried over magnesium sulfate. Removal of the solvent provides

the desired product as an orange solid, 2.6 g. m.p. 125-127°C. The analytical sample is recrystallized from pentane, m.p. 127-128°C.

Anal. Calc'd for $C_{17}H_{14}N_2F_2$: C, 71.8; H, 5.0; N, 9.9.

Found: C, 71.6; H, 5.1; N, 10.2.

The hydrochloride salt is prepared by bubbling hydrogen chloride into a solution of the free base in diethyl ether, m.p. 270-272°C.

PREPARATION C

*2-Benzyl-8-fluoro-5-(p-fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline*

To a stirred solution of 1.4 g. (4.9 mmoles) of 8-fluoro-5-(*p*-fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline and 1.02 g. (7.4 mmoles) of potassium carbonate in 10 ml. of dimethylformamide, heated to 60°C, is added dropwise 1.01 g. (5.9 mmoles) of benzyl bromide in 10 ml. of the same solvent. After heating for one hour, the reaction mixture is decanted into 200 ml. of an aqueous 2% potassium carbonate solution, and the resulting solution subsequently extracted (3 × 200 ml.) with benzene. The combined extracts are washed successively with water and a saturated brine solution, and dried over magnesium sulfate. The solvent is removed *in vacuo* and the residual oil which crystallizes on standing is triturated with hexane and filtered.

PREPARATION D

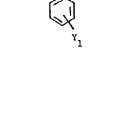
*8-Fluoro-5-(p-fluorophenyl)-2-[4-(p-fluorophenyl)-4-hydroxybutyl]-1,2,3,4-tetrahydro-γ-carboline hydrochloride*

1. To a stirred suspension of 2.84 g. (0.01 mole) of 8-fluoro-5-(*p*-fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline, 2.8 g. (0.01 mole) of ω-chloro-*p*-fluorobutyrophenone, 3.15 g. (0.03 mole) of sodium carbonate and a trace (50 mg.) of potassium iodide in 50 ml. of 4-methyl-2-pentanone gave, after heating at reflux for 15 hours followed by work-up of the reaction mixture as described in Preparation C, 2.6 g. of 8-fluoro-5-(*p*-fluorophenyl)-2-[3-*p*-fluorobenzoyl)propyl]-1,2,3,4-tetrahydro-γ-carboline free base, M.P. 150-155°C.

To 846 mg. (22.4 mmole) of sodium borohydride in 50 ml. of ethanol was added dropwise 2.5 g. (5.6 mmoles) of the γ-carboline obtained above in a warm solution of 80 ml. of ethanol and 20 ml. of tetrahydrofuran at such a rate that gentle reflux was maintained. After the addition was completed the mixture was heated at reflux for an additional hour, then cooled to room temperature. The supernatant was decanted into 300 ml. of water and the organic solvents removed from the aqueous phase by evaporation *in vacuo*. The residue was extracted with dichloromethane and the combined extracts washed with saturated brine and over magnesium sulfate. The solvent was evaporated *in vacuo* and the residue dissolved in a mixture of ethyl ether and dichloromethane. Hydrogen chloride gas was carefully bubbled into the solution until precipitation ceased. The title compound was recovered by filtration and dried, M. P. 249-250°C.

PREPARATION E

When 2-carbethoxy-1,2,3,4-tetrahydro-γ-carboline or 8-fluoro-2-carbethoxy-1,2,3,4-tetrahydro-γ-carboline are reacted with *o*-fluorobromobenzene or *m*-fluorobromobenzene by the method of Preparation B, Part II and the resulting 5-(*o* or *m*-fluorophenyl)-2-carbethoxy-1,2,3,4-tetrahydro-γ-carboline is hydrolyzed and decarboxylated by the procedure of Part III of Preparation B, the following compounds are obtained in like manner.



| $X_1$ | $Y_1$ |
|---|---|
| H | *o*-fluoro |
| H | *m*-fluoro |
| F | *o*-fluoro |
| F | *m*-fluoro |

PREPARATION F

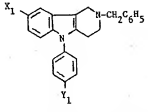
*5-(p-Fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline*

Equimolar amounts of phenylhydrazine and N-carbethoxy-4-piperidone are reacted by the procedure of Preparation B, Part I, to provide 2-carbethoxy-1,2,3,4-tetrahydro-γ-carboline. This is then reacted with *p*-fluorobromobenzene according to the procedure of Preparation B, Part II, and the product hydrolyzed by the procedure of Part III of Preparation B to obtain the title compound.

PREPARATION G

*8-Fluoro-5-phenyl-1,2,3,4-tetrahydro-γ-carboline*

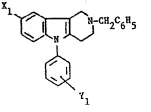
When *p*-fluorobromobenzene is replaced by an equivalent amount of bromobenzene in Part II of Preparation B and the resulting 2-carbethoxy-8-fluoro-5-phenyl-1,2,3,4-tetrahydro-γ-carboline is decarboxylated by the procedure of Part III of Preparation B, the title compound is similarly obtained.




When the product obtained in Preparation F is reacted with benzyl bromide by the procedure of Preparation C, the product obtained is of the above formula wherein $X_1$ is hydrogen and $Y_1$ is fluoro. Similarly, when the product of Preparation G is employed as starting material in the same procedure, a product of the above formula is obtained wherein $X_1$ is fluoro and $Y_1$ is hydrogen.

PREPARATION I

When the products of Preparation E are reacted with benzyl bromide by the procedure of Preparation C, the following compounds are similarly obtained.

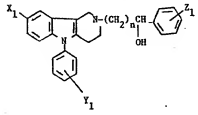



| $X_1$ | $Y_1$ |
|---|---|
| H | *o*-fluoro |
| H | *m*-fluoro |
| F | *o*-fluoro |
| F | *m*-fluoro |

PREPARATION J

Employing the appropriately substituted 5-phenyl-1,2,3,4-tetrahydro-γ-carboline and

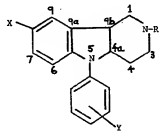
$Z_1C_6H_4CO(CH_2)_n$–A where A is Cl or Br as starting materials in each case in the procedure of Preparation D, the following compounds are similarly obtained.



| $n$ | $X_1$ | $Y_1$ | $Z_1$ |
|---|---|---|---|
| 3 | F | *p*-fluoro | *m*-fluoro |
| 3 | F | *p*-fluoro | H |
| 3 | H | *p*-fluoro | *p*-methoxy |
| 3 | F | H | *o*-methoxy |
| 3 | H | H | *p*-fluoro |
| 4 | F | *p*-fluoro | *p*-fluoro |
| 4 | F | *p*-fluoro | *p*-methoxy |
| 4 | F | *p*-fluoro | H |
| 4 | F | H | *o*-fluoro |
| 4 | F | H | *m*-methoxy |
| 4 | H | *p*-fluoro | *p*-fluoro |
| 4 | H | *p*-fluoro | H |
| 4 | H | H | H |
| 4 | H | *o*-fluoro | *p*-fluoro |
| 3 | H | *o*-fluoro | *p*-fluoro |
| 3 | F | *o*-fluoro | *p*-fluoro |
| 3 | H | *m*-fluoro | *m*-fluoro |
| 3 | F | *o*-fluoro | *p*-methoxy |
| 3 | H | *m*-fluoro | H |
| 4 | F | *o*-fluoro | *o*-fluoro |
| 4 | F | *m*-fluoro | *m*-methoxy |

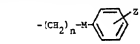
WHAT WE CLAIM IS:-

1. 2-substituted-5-aryl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indoles of the formula:

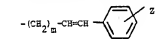


--- (I)

and the pharmaceutically acceptable salts thereof, wherein the hydrogen atoms in the 4a and 9b positions are in a *trans* relationship to each other and X and Y are the same or different and are each hydrogen or fluoro; R is $CH_3$ or a group of the formula:



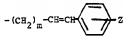
or



wherein n is 3 or 4, m is 2 or 3, M is

or

and Z is hydrogen, fluoro or methoxy; provided that when R is $CH_3$ at least one of X and Y is fluoro and when R is



Z is not hydrogen.

2. A compound according to claim 1 wherein R is a group of the formula

wherein n, m and Z are as defined in claim 1.

3. A compound according to claim 2 wherein M is

and n is 3.

4. The compound according to claim 3 wherein X and Y are each hydrogen and Z is *p*-fluoro.

5. A compound according to claim 3 wherein X and Y are each fluoro and Z is *p*-fluoro.

6. The compound according to claim 5 wherein Y is *p*-fluoro.

7. The compound according to claim 5 wherein Y is *o*-fluoro.

8. The compound according to claim 3 wherein X and Y are each hydrogen and Z is *p*-methoxy.

9. The compound according to claim 3 wherein X is fluoro, Y is *p*-fluoro and Z is *p*-methoxy.

10. The compound according to claim 3 wherein X, Y and Z are each hydrogen.

11. The compound according to claim 3 wherein X is fluoro, Y is *p*-fluoro and Z is hydrogen.

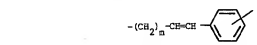
12. A compound according to claim 2 wherein M is

and n is 3.

13. The compound according to claim 12 wherein X and Y are each hydrogen and Z is *p*-fluoro.

14. The compound according to claim 12 wherein X is fluoro and Y and Z are each *p*-fluoro.

15. A compound according to claim 1 wherein R is a group of the formula



wherein m is as defined in claim 1 and z is fluoro or methoxy.

16. A compound according to claim 15 wherein X and Y are each fluoro, Z is *p*-fluoro and m is 2.

17. The compound according to claim 16 wherein Y is *p*-fluoro.

18. The compound according to claim 16 wherein Y is *o*-fluoro.

19. The compound according to claim 15 wherein X is fluoro, Y is *p*-fluoro, Z is *p*-methoxy and m is 2.

20. A compound according to claim 1 wherein R is a methyl group.

21. The compound according to claim 20 wherein X is fluoro and Y is *p*-fluoro.

22. *Trans*-8-fluoro-5-(*p*-fluorophenyl)-2-methyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido-[4,3-b]indole.

23. *Trans*-8-fluoro-5-(*p*-fluorophenyl-2-[4-hydroxy-4-(*p*-fluorophenyl) butyl]-2,3,4-4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

24. *Trans*-5-phenyl-2-[4-hydroxy-4-(*p*-methoxyphenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

25. *Trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-hydroxy-4-(*p*-methoxyphenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

26. *Trans*-5-phenyl-2-(4-hydroxy-4-phenylbutyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido-[4,3-b]indole.

27. *Trans*-8-fluoro-5-(*p*-fluorophenyl)-2-(4-hydroxy-4-phenylbutyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

28. *Trans*-5-phenyl-2-[3-(*p*-fluorobenzoyl)propyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

29. *Trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[3-(*p*-fluorobenzoyl)propyl]2,3,4,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

30. *Trans*-8-fluoro-5-(*p*-fluorophenyl)-2-[4-(*p*-fluorophenyl-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

31. *Trans*-8-fluoro-5-(*p*-fluorophenyl-2-[4-(*p*-methoxyphenyl)-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

32. *Trans*-8-fluoro-5-(*o*-fluorophenyl)-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

33. *Trans*-5-phenyl-2-[4-hydroxy-4-(*p*-fluorophenyl)butyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

34. *Trans*-8-fluoro-5-(*o*-fluorophenyl-2-[4-(*p*-fluorophenyl)-3-butenyl]-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole.

35. A process for preparing a compound of the formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof, substantially as hereinbefore described with reference to any one of Examples 3 or 4 and 7 to 15.

36. A pharmaceutical composition useful as a tranquilising agent which comprises a compound of the formula (I) as claimed in any one of claims 1 to 34 or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier.

37. A method for the treatment of schizophrenic manifestations in a non-human mammal which comprises orally or parenterally administering to a non-human mammal in need of such treatment a tranquilising amount of a compound of the formula (I) as claimed in any one of claims 1 to 34 or a pharmaceutical composition as claimed in claim 36.

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Agent for the Applicants.

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